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Iron-Catalyzed Methylation Using the Borrowing Hydrogen Approach

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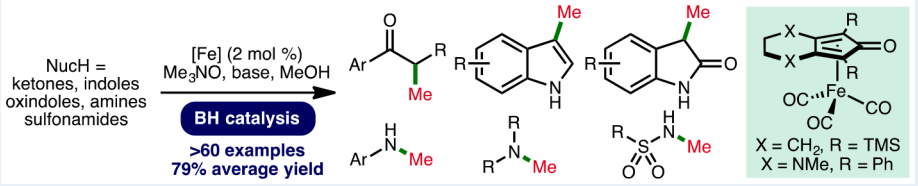
Supporting Information



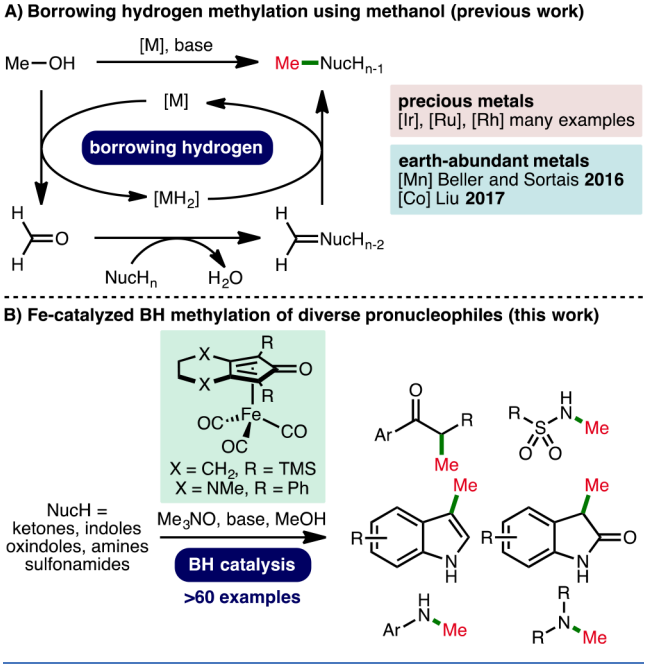
ABSTRACT: A general iron-catalyzed methylation has been developed using methanol as a C1 building block. This borrowing hydrogen approach employs a Knölker-type (cyclopentadienone)iron carbonyl complex as catalyst (2 mol %) and exhibits a broad reaction scope. A variety of ketones, indoles, oxindoles, amines, and sulfonamides undergo mono- or dimethylation in excellent isolated yields (>60 examples, 79% average yield).

KEYWORDS: *borrowing hydrogen, iron catalysis, methylation, methanol, mechanistic studies*

Methylation is a fundamental transformation in synthetic chemistry that is widely used for the synthesis and functionalization of fine chemicals.[1] Traditional methylation procedures often employ toxic and/or potentially explosive reagents including iodomethane, dimethyl sulfate, or diazomethane, among many others.[2] In recent years, methanol, an abundant and biodegradable liquid, has emerged as an attractive alternative reagent for methylation.[3] Borrowing hydrogen (BH), or hydrogen autotransfer, combines a transfer hydrogenation process with a concurrent reaction on the in situ-generated reactive intermediate.[4] This one-pot oxidation-reaction−reduction sequence has received much attention due to its inherent high atom economy and minimal waste generation,[5] allowing bench stable and inexpensive alcohols to be used as alkylating agents.[6] In comparison with benzyl and long-chain *n*-alkyl alcohols, it is challenging to use methanol as the alkylating agent in BH processes, due partly to the increased energy of dehydrogenation (ΔH (MeOH) = +84 kJ mol^{-1}, cf. ΔH (EtOH) = +68 kJ mol^{-1})[7] to form the required transient reactive formaldehyde intermediate.

Following the pioneering work of Grigg on the ruthenium- and rhodium-catalyzed methylation of arylacetonitriles and aromatic amines,[8] respectively, there have been a number of subsequent reports describing precious metal-catalyzed BH methylation (Scheme 1A).[9] Despite these advances, a key challenge in hydrogen transfer chemistry is the development and use of catalysts based on earth-abundant, inexpensive metals for more sustainable processes.[10] Considerable progress has been made in this regard, with well-defined iron, manganese, and cobalt catalysts being employed for a variety of homogeneous BH alkylation processes.[11] With the vast majority of reports primarily focusing on the use of benzyl alcohols as alkylating agents, Beller and Sortais have reported the methylation of aromatic amines using manganese pincer

Scheme 1. Previous Work and Outline of the Fe-Catalyzed BH Methylation Strategy



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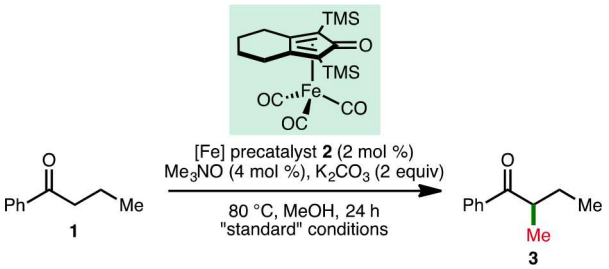
complexes.[12] Furthermore, Liu has recently disclosed a cobalt-based catalytic system for methylation.[13] However, the catalytic BH methylation using iron,[14] the most abundant transition metal in the Earth's crust, remains an unsolved problem. Herein, we report an efficient and general iron-catalyzed methylation of ketones, indoles, oxindoles, amines, and sulfonamides using methanol as a sustainable C1 building block (Scheme 1B).

To commence our studies, we selected butyrophenone **1** as a model substrate (Table 1). After extensive optimization,[15] it

Table 1. Optimization of Fe-Catalyzed BH Methylation[a]



entry	variation from "standard" conditions	yield[b] (%)
1	none	>98 (88)
2	no [Fe] precatalyst	<2
3	no Me_3NO activator	55
4	PPh_3 (4 mol %) instead of Me_3NO	37
5	2 mol % of Me_3NO	92
6	KOH (2 equiv) instead of K_2CO_3	93
7	KO*t*-Bu (2 equiv) instead of K_2CO_3	91
8	K_2CO_3 (0.5 equiv)	85
9	MeOH:toluene (1:1)	40
10	[**1**] = 0.2 M	94
11	[**1**] = 1 M	93
12	100 °C	94
13	60 °C	88
14[c]	[Fe] precatalyst **2** (1 mol %)	81

[a]Reactions performed using 1 mmol of ketone **1** and bench-grade MeOH. [**1**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]2 mol % of Me_3NO.

was found that a BH system composed of Knölker-type (cyclopentadienone)iron carbonyl precatalyst **2** (2 mol %),[16] trimethylamine *N*-oxide (4 mol %) to activate the catalyst,[17] K_2CO_3 (2 equiv) as base in MeOH ([**1**] = 0.5 M) at 80 °C for 24 h, enabled the methylation of **1**, giving **3** in 98% NMR yield and 88% isolated yield (entry 1). No methylation occurs in the absence of the iron precatalyst **2** (entry 2), with a significant reduction in conversion observed in the absence of trimethylamine *N*-oxide (entry 3). Substituting Me_3NO for PPh_3 as activator or lowering the loading of Me_3NO to 2 mol %, both result in decreased NMR yield of **3** (entries 4 and 5). Employing KOH or KO*t*-Bu as base, or using substoichiometric quantities of K_2CO_3 (0.5 equiv) all result in lower conversions to **3** (entries 6−8). Using methanol as solvent is crucial, with a mixed solvent system (MeOH:toluene (1:1)) resulting in only 40% NMR yield (entry 9). Altering the reaction concentration (entries 10 and 11), reaction temperature (entries 12 and 13), or reducing the catalyst loading to 1 mol % (entry 14), lowers the efficiency of the methylation of **1** to **3**.

The full scope of the Fe-catalyzed BH methylation process was explored, starting with the mono- and dimethylation of ketones (Scheme 2A).[18] Using the optimized reaction conditions (Table 1, entry 1) a variety of aryl alkyl substituted ketones were converted to the corresponding methylated products in excellent isolated yields (products **3**−**21**, 87% average yield). Acetophenone derivatives bearing α-alkyl (Me, Et, *n*-Pr, *n*-Bu, Bn), α-phenyl and α-heteroatom (OMe, OPh, NHPh) substitution undergo efficient methylation without cleavage of the carbon-heteroatom bonds within products **9**−**11**.[19] Within the aryl unit, 4-CF_3, 3-CF_3, and 2-CF_3 substitution is tolerated in addition to halide (4-Cl) and electron-donating (4-OMe) substituents. Hindered extended aromatic systems (1-Np) and heteroaryls (2-furanyl, 2-thiophenyl and 3-pyridyl) can also be present within the ketone. The monomethylation procedure performs well upon scale-up, with the formation of **3** successfully carried out on a 10 mmol scale in 99% (1.61 g) isolated yield. 5-, 6-, and 7-membered cyclic ketones also undergo methylation, using KO*t*-Bu (10 mol %) as base, giving products **22**−**24**. A representative selection of acetophenone derivatives, which are unsubstituted at the α-position, undergo dimethylation using 2 equiv of KO*t*-Bu at 110 °C in high isolated yields (products **4**, **13**, **16**, **17**, and **25**−**27**, 74% average yield). The catalytic system tolerated the reducible benzyl ether moiety within **26**. Selectivity considerations exist when employing ketones that are enolizable at both α-positions. Phenyl acetone, 1-phenylbutan-2-one, and dibenzyl ketone undergo selective monomethylation at 80 °C, giving **28**, **29**, and **30** in 50%, 58%, and 57% isolated yields, respectively. For phenyl acetone and 1-phenylbutan-2-one, monomethylation occurs preferentially at the more acidic benzylic position.

Next, we explored the use of indoles and oxindoles as substrates for the Fe-catalyzed BH methylation process (Scheme 2B/C). Using 2 equiv of K_2CO_3 as base, a variety of indoles undergo *C*(3)-methylation in high isolated yields (products **31**−**36**, 78% average yield).[20] In addition to unsubstituted indole, methyl and halide substituents are tolerated at the 2-, 4-, 5-, 6-, and 7-positions. Furthermore, by employing CD_3OD as solvent, d_3-skatole **37**, which has utility in studying metabolism kinetics,[21] was accessed in 67% yield. Oxindoles, a class of activated amide, also undergo facile *C*(3)-methylation at 110 °C (products **38**−**44**, 77% average yield). *N*-Methyl, *N*-benzyl, and *N*-phenyl substitution is tolerated in addition to various halide substitutions at the 5-position. This is the first example of borrowing hydrogen *C*-methylation of an amide using a homogeneous catalytic system.[22]

We also investigated the Fe-catalyzed BH *N*-methylation of amines using methanol (Scheme 2D). Using the optimized reaction conditions (Table 1, entry 1), a variety of arylamines undergo monomethylation in high isolated yields (products **45**−**50**, 74% average yield). Within the aryl unit, electron-donating (4-OMe) substituents are tolerated in addition to halides (4-Br, 4-Cl), hindered aromatic systems (2-Me), and heteroaryls (3-pyridyl).[23] A selection of cyclic and acyclic secondary amines also undergo efficient *N*-monomethylation, accessing the corresponding tertiary amines in high yields (products **51**−**55**, 78% average yield). Finally, employing Renaud's (cyclopentadienone)iron carbonyl precatalyst **61** (4 mol %),[24] which contains a more electron-rich cyclopentadienone framework, the *N*-monomethylation of sulfonamides was also demonstrated (products **56**−**59**, 83% average

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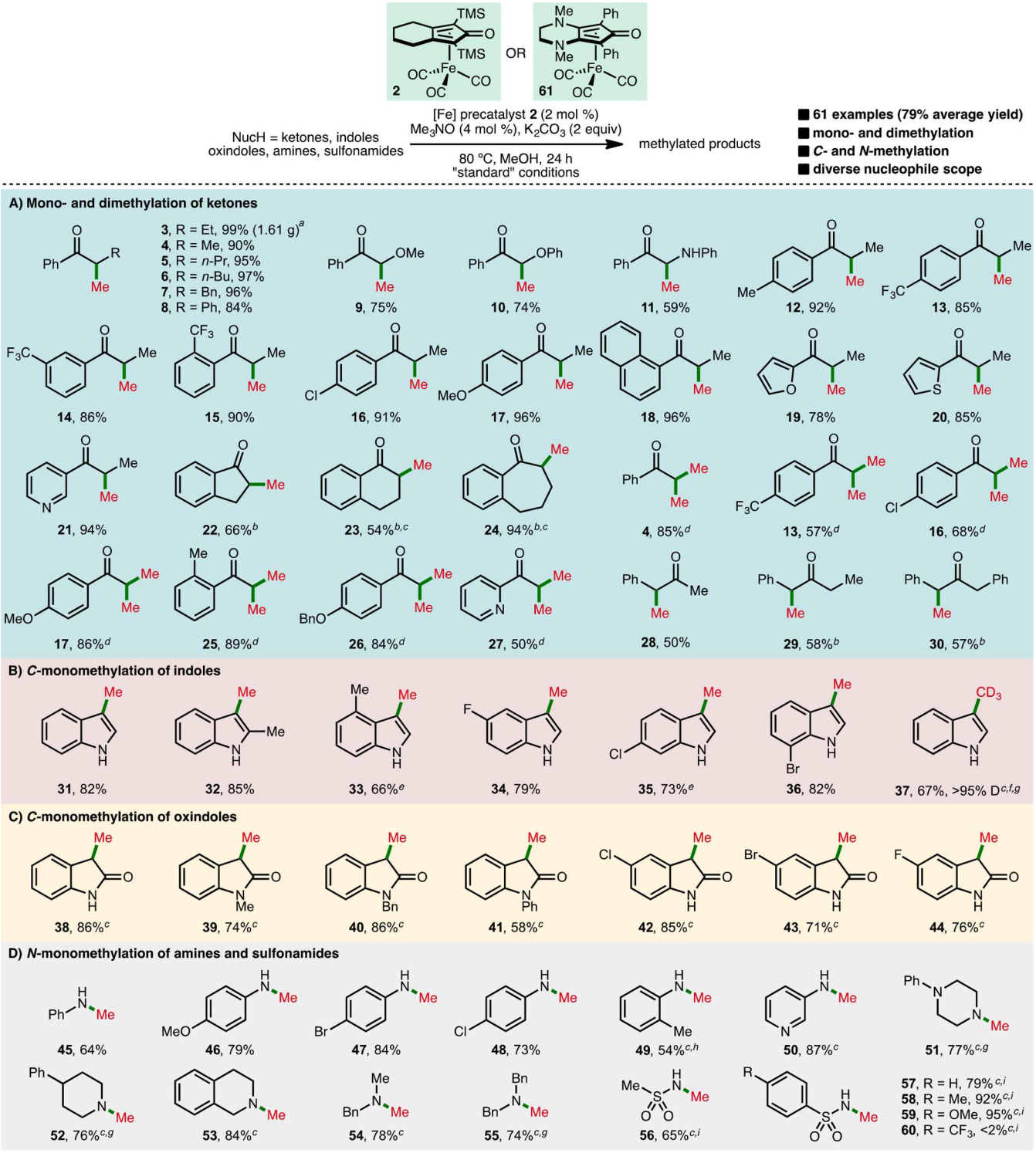
Scheme 2. Scope of the Fe-Catalyzed BH Methylation Process[§]



[§]Reactions performed using 1 mmol of ketone, indole, oxindole, amine or sulfonamide starting material. All yields are isolated yields after chromatographic purification Reagents and conditions: [a]10 mmol of ketone starting material; [b]KO*t*-Bu (10 mol %); [c]110 °C; [d]KO*t*-Bu (2 equiv); [e]48 h; [f]CD_3OD as solvent; [g][Fe] precatalyst **2** (4 mol %), Me_3NO (8 mol %); [h]96 h; [i][Fe] precatalyst **61** (4 mol %), Me_3NO (8 mol %).

yield). Methanesulfonamide and sulfonamides containing electron-rich aromatic rings all undergo efficient *N*-methylation, whereas 4-$CF_3C_6H_4$ substituted sulfonamide **60** was unreactive.

Selecting the monomethylation of propiophenone as a representative reaction, a number of experiments were performed in order to obtain mechanistic insight (Scheme 3). First, the validity of several proposed intermediates (*β*-hydroxy ketone **62**, methyl ether **63**, diketone **64**, and enone **65**) was probed by subjecting them to the "standard" methylation reaction conditions (Scheme 3A). Conjugate addition of methanol or the enolate of propiophenone to

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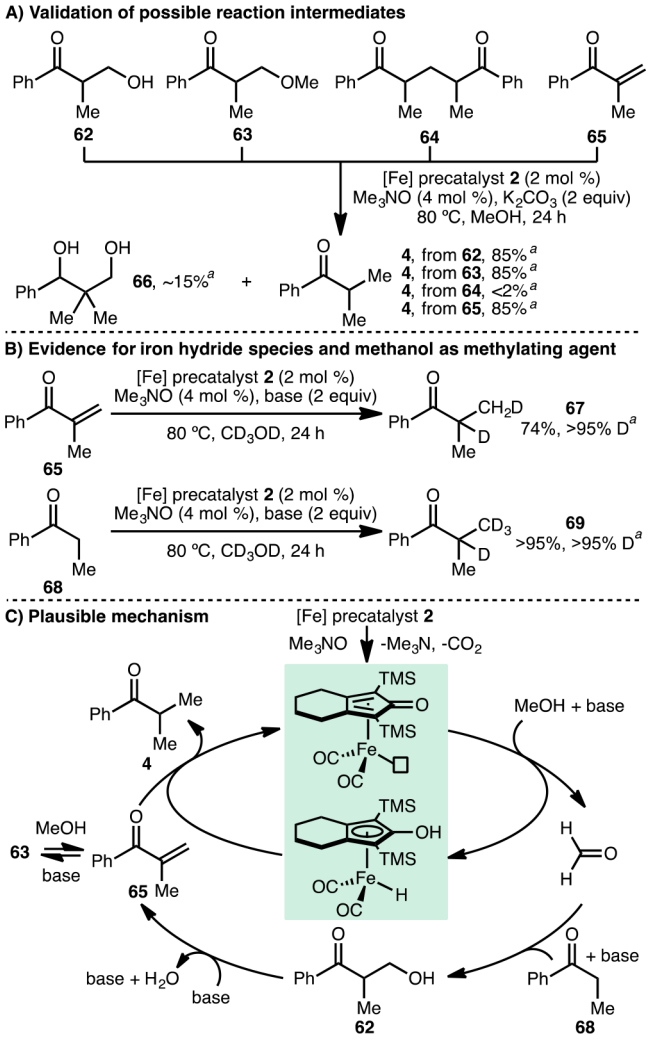
Scheme 3. Mechanistic Considerations



[a]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

enone **65**, would result in the formation of **63** and **64**, respectively. Compounds **62**, **63**, and **65** were all converted to **4** in 85% NMR yield, indicating that they are all plausible reaction intermediates. The remaining mass balance in these reactions (~15%) was diol **66**, which likely forms via conjugate addition of the iron hydride species to **65**, followed by trapping of the resulting enolate with formaldehyde and subsequent hydrogenation.[25] Diketone **64** was returned after 24 h, indicating that this is a nonproductive reaction pathway and that **64** does not lead to the formation of **4**. To gain further mechanistic insight, employing CD_3OD as solvent under the otherwise standard reaction conditions, enone **65** was converted to **67** (74%, > 95% D) providing evidence for the proposed iron hydride species (Scheme 3B). Furthermore, propiophenone **68** was converted to **69** (>95%, > 95% D), confirming that methanol is the source of the methyl group. As such, the proposed mechanism begins with CO decoordination by Me_3NO to form the active iron complex, which abstracts hydrogen from methanol in the presence of base to form the required transient reactive formaldehyde intermediate (Scheme 3C). A subsequent aldol reaction with propiophenone generates β-hydroxy ketone **62** that undergoes base-catalyzed dehydration to form enone **65**, which may exist in equilibrium with **63**. Finally, reduction of enone **65** by the iron−hydrogen complex gives methylated product **4** with regeneration of the active iron complex.

In conclusion, we have developed a general and efficient Fe-catalyzed methylation using methanol as a sustainable C1 building block via the borrowing hydrogen approach. A diverse array of ketones, indoles, oxindoles, amines, and sulfonamides undergo mono- or dimethylation in excellent isolated yields (61 examples, 79% average yield). Mechanistic experiments provided evidence for plausible reaction intermediates, an iron-hydride species, and methanol as themethylating agent in this catalytic process. Ongoing studies are focused on further applications of earth-abundant transition metals in catalysis, and these results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b02158.

Optimization data, experimental procedures, characterization of new compounds, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

Information about the data that underpins the results presented in this article, including how to access them, can be found in the Cardiff University data catalogue at http://doi.org/10.17035/d.2018.0051041048 (accessed June 14, 2018)

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